REMARKS

Claims 1-2, 5-8,11-13, 15, 18-20, 22-24 and 41-49 are pending. Claims 25-40 have been cancelled without prejudice or disclaimer as being drawn to non-elected inventions. Claims 3-4, 9-10, 14, 16, 17 and 21, were canceled, claims 1, 5, 7-8, 15, 19 and 22 were amended, and new claims 41-49 were added. The specification was amended to include SEQ ID NOs and to replace the pending sequence listing with the enclosed sequence listing in compliance with 37 C.F.R. 1.821-825. Support for the amendment to claims 1 and 7 can be found in the specification as filed, *e.g.*, at page 19, lines 13-15 and Table 1. Support for the amendment to claim 8 can be found in the specification as filed, *e.g.*, at page 2, lines 11-14; page 19, lines 13-15; Table 1; and Figure 3. Support for the amendment to claim 15 can be found in the specification as filed, *e.g.*, Table 1 and Figure 3. Support for the amendment to claim 22 can be found in the specification as filed, *e.g.*, at page 19, lines 13-15 and Table 1. Support for new claims 41-48 can be found in the specification as filed, *e.g.*, at page 19, lines 13-15; Table 1; Figure 3; and in originally filed claims 7, 13, and 19. No new matter has been added by these amendments.

Information Disclosure Statement.

The Examiner has indicated that reference C1 (GenBank Accession No. E00029) in the Information Disclosure Statement filed on September 17, 2002 was not received by the USPTO. In response, Applicants note that a copy of this reference in enclosed herewith.

Rejection Under 35 USC § 112, first paragraph

Claims 1-24 are rejected for lack of enablement The Examiner states that the specification "does not reasonably provide enablement for "all" possible compositions comprising glycosylated mutants of IFN-β coupled to polyethylene glycol." (See Office Action.

page 3). Claims 3-4, 9-10, 14, 16, 17 and 21 were cancelled. Applicants traverse this rejection as it applies to the remaining claims as amended.

First, Applicants have amended claims 1, 5, 8, 15, and 22 herein to specifically recite the amino acid sequence of SEQ ID NO:25, which corresponds to the wild-type interferon-beta-1a polypeptide.

Second, Applicants have amended claim 7 herein to specifically recite the amino acid sequence of SEQ ID NO:26, which corresponds to the A1 mutein of interferon-beta-1a.

The wild-type interferon-beta-1a polypeptide and the A1 mutein of interferon-beta-1a are fully disclosed at, *e.g.*, Table 1 and Example 1. Therefore, Applicants assert that the claims as amended herein are fully enabled by the specification as filed. Thus, this rejection should be withdrawn.

Rejection Under 35 USC § 112, second paragraph

Claims 3, 7, and 8-21 are rejected for indefiniteness. Claims 3, 9-10, 14, 16, 17 and 21 were cancelled. Applicants traverse this rejection as it applies to the remaining claims as amended.

The Examiner states that claims 3 and 7 are indefinite because the claims recite the phrases "higher antiviral activity" and "greater antiviral activity." (See Office Action, page 5). Claim 3 was cancelled and claim 7 has been amended herein to delete the phrases "higher antiviral activity" and "greater antiviral activity."

The Examiner also states that claims 8 and 15 are indefinite because the claims recite the phrases "enhanced activity" and "substantially similar activity." (See Office Action, page 5). Claim 8 has been amended herein to recite in part "an activity at least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by antiviral activity." Further, claim 15 has been amended herein to recite in part "the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral activity."

Applicants assert that claims 7, 8 and 15 as amended herein are definite. Thus, this rejection should be withdrawn.

Rejection Under 35 USC § 102

Claims 1-2 and 15-16 are rejected as being anticipated by Katre et al (WO 87/00056) ("Katre"). The Examiner states that "the INF-β disclosed by Katre et al is a mutant that has the cysteine at position 17 replaced with a serine."

Katre discloses interferon-beta-1b. Applicants have amended the pending claims herein to recite interferon-beta-1a. Specifically, Applicants have amended claims 1, 5, 8, 15, and 22 herein to specifically recite the amino acid sequence of SEQ ID NO:25, which corresponds to the wild-type interferon-beta-1a polypeptide. Applicants have also amended claim 7 to specifically recite the amino acid sequence of SEQ ID NO:26, which corresponds to the A1 mutein of interferon-beta-1a. This mutein has the amino acids at positions 2, 4, 5, 8 and 11 of the wild-type interferon-beta-1a polypeptide replaced with alanines; the cysteine at amino acid 17 is undisturbed. As such, Katre does not anticipate the claims as amended, and this rejection can be withdrawn.

Rejection Under 35 USC § 103(a)

Claim 19 is rejected as being obvious over Katre in view of Capon et al. (US Patent 5,116,964) ("Capon"). The Examiner states that "Capon et al teach chimeric polypeptides comprising ligand binding partners fused to stable plasma proteins."

Katre discloses interferon-beta-1b, not the wild-type interferon-beta-1a polypeptide required by amended claim 19. Capon does not cure this deficiency. Capon does not teach or suggest the use of any interferon polypeptide, much less the specific wild-type interferon-beta-1a polypeptide recited in the pending claim 19. As such, claim 19 as amended herein is unobvious in view of Katre and Capon. This rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact Applicant's undersigned attorney at the telephone number indicated below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning on page 16, line 19 was amended as follows:

-- We found unique site(s) for polymer attachment that would not destroy function of the interferon-beta-1a. In addition, we also used site-directed mutagenesis methods to independently investigate site(s) for polymer attachment (See Example 1). Briefly, we undertook a mutational analysis of human interferon-beta-1a with the aim of mapping resides required for activity and receptor binding. The availability of the 3-D crystal structure of human interferon-beta-1a (see above and Example 1) allows us to identify, for alanine (or serine) substitutions, the solvent-exposed residues available for interferon beta receptor interactions, and to retain amino acids involved in intramolecular bonds. A panel of fifteen alanine scanning mutations were designed that replaced between two and eight residues along distinct regions of each of the helices (A (A1 (SEQ ID NO:26), A2 (SEQ ID NO:27)),B (B1 (SEQ ID NO:31), B2 (SEQ ID NO:32), C (C1 (SEQ ID NO:33), C2 (SEQ ID NO:34)), D (SEQ ID NO:37), E (SEQ ID NO:40)) and loops (AB1 (SEQ ID NO:28), AB2 (SEQ ID NO:29), AB3 (SEQ ID NO:30), CD1 (SEQ ID NO:35), CD2 (SEQ ID NO:36), DE1 (SEQ ID NO:38), DE2 (SEQ ID NO:39)) of interferon-beta-1a (SEQ ID NO: 25). See Example 1. --

In the Claims:

Claims 1, 5, 7-8, 15, 19 and 22 were amended as follows:

1. (Amended) A composition comprising the [a] glycosylated interferon-beta-1a of SEQ ID NO: 25 coupled to a non- naturally-occurring polymer at an N-terminal end of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety.

3-4. (Cancelled).

5. (Amended) The composition of claim 1, wherein the interferon -beta-1a of SEQ ID NO: 25 is an interferon -beta-1a fusion protein.

7. (Amended) A composition comprising the glycosylated interferon-beta-1a of SEQ ID NO: 26 coupled to a non- naturally-occurring polymer at the N-terminus of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety [The composition of claims 1 or 5, wherein the interferon beta is a mutant interferon beta having at least one of the following properties: (a) the mutant has a higher antiviral activity than wild type interferon-beta- 1a, wherein the antiviral activity is measured by viral induced lysis of cells; (b) the mutant has, relative to wild type interferon -beta- 1a, greater antiviral activity than antiproliferative activity; (c) the mutant binds interferon receptor but has, when compared to wild type interferon - beta-1a, lowered antiviral activity and lowered antiproliferative activity relative to receptor binding activity].

8. (Amended) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 coupled to a polymer comprising a polyalkylene glycol moiety, wherein the interferon -beta- 1a is coupled to the polymer at a site on the interferon-beta-1a that is an N- terminal end, wherein the physiologically active interferon -beta 1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon -beta composition has an [enhanced] activity at least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by an antiviral assay.

9-10. (Cancelled).

14. (Cancelled).

15. (Amended) A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 N-terminally coupled to a polymer comprising a polyalkylene glycol moiety,

wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal [substantially similar] activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

16-17. (Cancelled).

19. (Amended) The composition of claim 15, wherein the interferon-beta-1a is an interferon beta fusion protein.

21. (Cancelled).

22. (Amended) A stable, aqueously soluble, conjugated interferon-beta-1a complex comprising a interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 N-terminally coupled to a polyethylene glycol moiety, wherein the interferon-beta-1a is coupled to the polyethylene glycol moiety by a labile bond, wherein the labile bond is cleavable by biochemical hydrolysis and/or proteolysis.

41. (New) The composition of claim 7, wherein the glycosylated interferon-beta-1a of SEQ ID NO: 26 is an interferon-beta-1a fusion protein.

42. (New) The composition of claim 41, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

43. (New) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 26 coupled to a non- naturally-occurring polymer at the N-terminus of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has an activity at

least 2-fold greater relative to physiologically active interferon-beta-lb, when measured by an antiviral assay.

44. (New) The composition of claim 43, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

45. (New) The composition of claim 44, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

46. (New) A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a, comprising the amino acid sequence of SEQ ID NO: 25, N-terminally coupled to a polymer comprising a polyalkylene glycol moiety, wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

47. (New) The composition of claim 46, wherein the interferon-beta-1a is an interferon beta fusion protein.

48. (New) The composition of claim 47, wherein the interferon beta fusion protein comprises a portion of an immunoglobulin molecule.